

Recent Topics of Hyperuricemia for Metabolic Syndrome, Cardiovascular, and Chronic Renal Diseases

Hiroshi Bando^{1,2*}

¹Tokushima University / Medical Research, Tokushima, Japan

²Japan Low Carbohydrate Diet Promotion Association, Kyoto, Japan

*Corresponding author: Bando H, Tokushima University/ Medical Research, Tokushima, Nakashowa 1-61, Tokushima 770-0943 Japan; Tel: +81-90-3187-2485; E-mail: pianomed@bronze.ocn.ne.jp

Received: February 25, 2020; **Accepted:** March 03, 2020; **Published:** March 10, 2020

Abstract

Hyperuricemia and gout have been important diseases, which have close relationship with metabolic syndrome, cardiovascular, and chronic kidney diseases. Oral medicine for treatment includes febuxostat and allopurinol. Both agents have been compared as urate-lowering therapy for the influence of cardiovascular and renal risk factors. Some papers showed no difference for the major adverse cardiac events (MACEs) between both agents. However, there have been controversies concerning the benefit and risk of them. Further evaluation would be necessary and expected for future research.

Keywords: *Hyperuricemia; Gout; Chronic kidney disease (CKD); Febuxostat; Allopurinol*

The increasing health and medical problem in the world would be metabolic syndrome. It currently includes obesity, hypertension, diabetes, and dyslipidaemia. However, patients with metabolic syndrome have also shown problems concerning hyperuricemia and gout [1]. Therefore, adequate management of hyperuricemia at present and in the future would be necessary.

On the other hand, chronic kidney disease (CKD) has also become crucial disease [2]. In addition to hypertension and diabetes, hyperuricemia may be involved in the deterioration of renal function.

From both of the viewpoints above, it is important to pay attention to serum uric acid in the clinical practice. Several current topics about these problems are described in this article.

The incidence of gout has been increasing across the world. It has been more than doubled over the recent 20 years, in which the incidence rate ratio would be 2.62 [3]. This increasing status of gout has been observed associated with more frequent

occurrence of metabolic syndrome, cardiovascular and renal risk factors, where these tendencies would become a significant public health challenge [3].

Gout and hyperuricemia may cause various impaired functions of cardiovascular and renal organs. Some studies among gout, hyperuricemia, cardiovascular disease, CKD have been reported so far [4]. Well-known medical agents for gout and hyperuricemia include febuxostat and allopurinol. From recent journals, several topics would be described as i) febuxostat, ii) allopurinol, iii) febuxostat vs allopurinol in this order.

There was a report about febuxostat. A randomized, double-blind, placebo-controlled trial was conducted for 467 patients with stage 3 CKD and asymptomatic hyperuricemia at 55 multi centers in Japan [5]. They were assigned to receive febuxostat or placebo for 108 weeks. As the primary end point, no significant difference was found in mean eGFR slope in both groups. There was a significant benefit in febuxostat group without proteinuria ($p=0.005$) and lower creatinine value than the median ($p=0.009$). Gouty arthritis was significantly lower ($p=0.007$) in febuxostat group (0.9%) compared with placebo group (5.9%). Adverse events were not found in febuxostat group. Consequently, febuxostat group did not mitigate the decline of renal function for patients with stage 3 CKD and asymptomatic hyperuricemia.

A retrospective, population-based cohort study was observed for allopurinol [6]. The subjects were about 38,000 diabetic patients with follow-up of 4.7 years in median. Allopurinol was associated with a reduction in the primary outcome (adjusted hazard ratios (aHR) 0.77 and 0.81 for males and females, respectively). There was marked reductions in all-cause mortality and modest reductions in cardiovascular events/ chronic heart failure (CHF). Further, allopurinol was associated with reduced risk of pneumonia in males (aHR 0.88).

Comparison papers have been found between febuxostat or allopurinol. There was a multicenter, double-blind, noninferiority trial involving patients with gout and cardiovascular disease [7]. Subjects were 6190 patients, who were provided febuxostat or allopurinol for 32 months in median. There was no significant difference in a primary end-point event. However, all-cause and cardiovascular mortality were significantly higher in the febuxostat group than in the allopurinol group. The hazard ratio was 1.22 and 1.34, respectively.

As a result, the US Department of Health, Labor and Welfare and the Pharmaceuticals and Medical Devices Agency (PMDA) have revised the comment. They suggested that febuxostat would be restricted to allopurinol-incompatible patients by the recommendation of the FDA.

On the other hand, there are papers showing no significant difference. There was a population-based cohort study and meta-analysis for 17687 patients receiving febuxostat or allopurinol during 5 years [8]. Febuxostat group showed no significant increased risk for cardiovascular event (HR 1.16) or related death (HR 1.49) compared to allopurinol group. The result of the meta-analysis also showed a consistent result. Further, the incidence and severity in febuxostat-hypersensitivity are significantly lower than with allopurinol (0.2 vs 2.7, $p<0.001$).

A cohort study of cardiovascular risk for febuxostat and allopurinol was found in about 50000 patients [9]. The primary outcome included myocardial infarction, stroke/transient ischaemic attack (TIA), or coronary revascularization, which showed 1.84 vs 1.89 of incidence rate per 100 person-years for two groups. There was no significant difference for the secondary outcomes, such as all-cause mortality.

The risk of cardiovascular events and mortality was compared between febuxostat and allopurinol use [10]. The total subjects were 270,423 patients, and data were used from the Taiwan National Health Insurance Research Database. Febuxostat group showed significantly higher risk for heart failure hospitalization (HR 1.22), atrial fibrillation hospitalization (HR 1.19), and CV death (HR: 1.19) than allopurinol group. In contrast, there was no difference for the major adverse cardiac events (MACEs) composite endpoint, venous thromboembolism, myocardial infarction, ischemic stroke, and all-cause mortality. The elevated risk of heart failure hospitalization was consistent throughout the primary and sensitivity analyses.

There was a study to compare two agents of febuxostat and allopurinol on cardiovascular mortality for in elderly patients with chronic heart failure [11]. Febuxostat (n=120) and allopurinol (n=135) were balanced for most of the baseline variables. After 5.1 years of follow-up, the cumulative cardiovascular survival was 0.96 vs 0.89, respectively (adjusted, significant, $p=0.04$). These results suggest that febuxostat may favorably affect cardiovascular mortality in comparison with allopurinol in elderly patients with mild-to-moderate heart failure.

Next, there are various discussions as to whether hyperuricemia worsens renal dysfunction. In order to assess the influence of allopurinol for the risk of developing chronic kidney disease stage 3 or higher, there was a time-stratified propensity score-matched, population-based, prospective cohort study [12]. The subjects were newly diagnosed gout who initiated allopurinol, besides there was control subjects who did not initiate allopurinol. These data were from the Health Improvement Network (THIN), a United Kingdom general practitioner electronic health records database.

As a result of more than 9000 subjects included, use of allopurinol of at least 300 mg/day brought lower risk of developing CKD stage 3 or higher in comparison with non-users. HR was 0.87 (95% CI, 0.77-0.97). In contrast, allopurinol initiation less than 300mg/day did not show renal function decline (HR 1.00). This large cohort showed more than 300mg/day of allopurinol initiation has lower risk of renal function deterioration [12]. Consequently, physicians would consider evaluating other potential causes when gout patients have renal function decline.

The prevalence of CKD and hyperuricemia has been steadily increasing. There was the KoreaN cohort Study for Outcomes in patients with Chronic Kidney Disease (KNOW-CKD), a prospective cohort study with totally 2042 patients with CKD [13]. They were classified into quartiles on the basis of uric acid value and CKD level. The progression risk to renal failure was increased by 28% (HR 1.277) for 1mg/dl increase of the baseline uric acid.

In multivariate models, an association was found between the highest quartile of uric acid and increased risk of composite renal outcome (HR 3.590). Both febuxostat and allopurinol did not affect the renal outcome. Consequently, hyperuricemia seemed to be independent risk factor for composite renal outcome, and febuxostat and allopurinol did not show protective effect for renal function [13].

There was a review concerning how to manage asymptomatic hyperuricemia. Hyperuricemia and gout may be a cause or a consequence of a comorbidity. Although hyperuricemia may be linked to metabolic, cardiovascular and renal comorbidities by epidemiological studies, these links are not proved to be causal by Mendelian randomization investigations [14]. There have been controversy and discrepancy for urate-lowering therapy (ULT) for asymptomatic hyperuricemia. The risk/benefit ratio of ULT has been unclear. However, the following therapies have seemed to be useful, including weight loss as appropriate, therapeutic lifestyle changes, and sufficient physical activity [14].

In the actual clinical practice, physicians have managed many patients with hyperuricemia and gout. Gout has been characterized for its elevated uric acid and arthritis [15]. It is often associated with metabolic syndrome and obesity. There was an analysis of 5,233 patients from 20 studies. Mean value of uric acid was 6.5 mg/dL at pre-bariatric surgery. A decrease of uric acid was observed 0.73 mg/dL in 3 months, and 1.91 mg/dL in 3 years [15].

The number of the patients with gout has been increasing [16]. According to National Health Service (NHS) Digital Hospital Episode Statistics data, the incidence of unplanned gout admission was increased by 58.4% during 10 years. They were 7.9 to 12.5 admissions from 2006/7 to 2016/17, which showed significant difference per 100,000 population a year ($p < 0.0001$). Community prescriptions were increased for allopurinol and colchicine by 71.4% and 165.6%, respectively. Moreover, febuxostat prescription was increased 20-fold since 2010 [16].

In summary, hyperuricemia and gout have been the important issues to be managed in clinical practice. It would be necessary to evaluate cardiovascular risk and renal function for the treatment of febuxostat and allopurinol. We hope that this article will serve as a reference for future clinical and research studies.

REFERENCES

1. Zhang X and Lerman LO. The metabolic syndrome and chronic kidney disease. *Transl Res.* 2017;183:14-25.
2. Johnson RJ, Bakris GL, Borghi C, et al. Hyperuricemia, Acute and Chronic Kidney Disease, Hypertension, and Cardiovascular Disease: Report of a Scientific Workshop Organized by the National Kidney Foundation. *Am J Kidney Dis.* 2018;71(6):851-65.
3. Elfishawi MM, Zleik N, Kvrqic Z, et al. The Rising Incidence of Gout and the Increasing Burden of Comorbidities: A Population-based Study over 20 Years. *J Rheumatol.* 2017;45(4):574-79.
4. Foody J, Turpin RS, Tidwell BA, et al. Major Cardiovascular Events in Patients with Gout and Associated Cardiovascular Disease or Heart Failure and Chronic Kidney Disease Initiating a Xanthine Oxidase Inhibitor. *Am Health Drug Benefits.* 2017;10(8): 393-401.
5. Kimura K, Hosoya T, Uchida S, et al. Febuxostat Therapy for Patients with Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial. *Am J Kidney Dis.* 2018;72(6):798-810.
6. Weisman A, Tomlinson GA, Lipscombe LL, et al. Association between allopurinol and cardiovascular outcomes and all-cause mortality in diabetes: A retrospective, population-based cohort study. *Diabetes Obes Metab.* 2019;21(6):1322-9
7. White WB, Saag KG, Becker MA, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. *N*

Engl J Med. 2018;378(13):1200-10.

8. Chen CH, Chen CB, Chang CJ, et al. Hypersensitivity and cardiovascular risks related to allopurinol and febuxostat therapy in Asians: A population-based cohort study and meta-analysis. *Clin Pharmacol Ther.* 2019;106(2):391-401.
9. Kang EH, Choi HK, Shin A, et al. Comparative cardiovascular risk of allopurinol versus febuxostat in patients with gout: a nation-wide cohort study. *Rheumatol.* 2019;58(12):2122-9.
10. Su CY, Shen LJ, Hsieh SC, et al. Comparing Cardiovascular Safety of Febuxostat and Allopurinol in the Real World: A Population-Based Cohort Study. *Mayo Clin Proc.* 2019;94(7):1147-57.
11. Cicero A FG, Cosentino ER, Kuwabara M, et al. Effects of allopurinol and febuxostat on cardiovascular mortality in elderly heart failure patients. *Intern Emerg Med.* 2019;14(6):949-56.
12. Vargas-Santos AB, Peloquin CE, Zhang Y, et al. Association of Chronic Kidney Disease with Allopurinol Use in Gout Treatment. *JAMA Intern Med.* 2018;178(11):1526-33.
13. Oh TR, Choi HS, Kim CS, et al. Hyperuricemia has increased the risk of progression of chronic kidney disease: propensity score matching analysis from the KNOW-CKD study. *Sci Rep.* 2019;9(1):6681.
14. Chalès G. How Should We Manage Asymptomatic Hyperuricemia? *Joint Bone Spine.* 2019;86(4):437-43.
15. Yeo C, Kaushal S, Lim B, et al. Impact of bariatric surgery on serum uric acid levels and the incidence of gout-A meta-analysis. *Obes Rev.* 2019;20(12):1759-70.
16. Russell M, Yates M, Bechman K, et al. Return of the King: Rising Incidence of Acute Hospital Admissions due to Gout. *J Rheumatol.* 2019;47(3):190257.